Evaluation of Macular Ischemia in Diabetic Patients by Optical Coherence Tomography Angiography & Fundus Fluorescein Angiography

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Abstract: Purpose: To evaluate the characteristics of Diabetic Macular Ischemia DMI showed on OCTA in comparison to conventional fluorescein angiography in DR patients and to highlight the utility of OCTA in detection of DMI concerning its advantages and disadvantages in comparison to fluorescein angiography. **Design:** prospective cross-sectional, observational study. **Methods:** A total of 20 eyes of 12 patients (with a known clinical diagnosis of DR; in the non proliferative stage) and 6 eyes of normal subjects, were recruited. All patients underwent standard ophthalmological examination together with multimodal imaging procedures including; color fundus photography, fluorescein angiography and optical coherence tomography angiography using a Zeiss Cirrus 5000 HD-OCT (Zeiss Meditec. Inc, Germany) machine. All imaging procedures were performed on the same day or during the same week. Quantitative flow analysis of the SCP has been performed for selected 20 images of 12 eyes (18 with moderate NPDR and 2 with mild NPDR) versus 6 eyes of normal controls. **Results:** In this study, we assessed whether OCT angiography can detect changes in FAZ shape and size in comparison with FA image at the same time. Furthermore, the superficial and deep vasculature surrounding the FAZ was analyzed in DR in comparison to a healthy control group. In addition, we were interested to know if these FAZ alterations correlate with visual acuity and can be used for early screening. We found that Statistical analysis shows that there was statistically significant difference between FAZ area size measurements in mm^2 by FFA (mean value 0.83 ± 0.33) and SCP (mean value 0.45 ± 0.14) in OCTA among patients group that was larger in FFA (P-value < 0.01: Highly significant). On the other hand, no statistically significant difference was found among control group (mean FAZ size in FFA 0.23 ± 0.03 and mean FAZ size in SCP OCTA 0.19 ± 0.03 with P-value > 0.05: Non significant). We also found that statistical analysis shows that there was statistically significant difference between control group and patients group regarding FAZ area size measurements in mm^2 by FFA and OCTA in (SCP & DCP) that was larger in patient group (Mean FAZ size by FFA in control group 0.23 ± 0.03 and patient group 0.83 ± 0.33 with P-value < 0.01: Highly significant) and (Mean FAZ size by SCP OCTA in control group 0.19 ± 0.03 and patient group 0.45 ± 0.14with P-value < 0.01: Highly significant). We finally found negative correlation between BCVA and FAZ area size in DCP of OCTA which was important result in our study as a prognostic sign before and after treatment. **Conclusion:** OCT angiography is one of the first non-invasive imaging techniques capable of detecting changes in the FAZ. OCT angiography data showed that in the superficial layer of the vasculature, the mean horizontal, vertical, maximum FAZ diameter were larger in diabetic eyes than in healthy eyes. These findings correspond to our data based on funduscopy and FA. Moreover, all of the above-mentioned findings are more obvious in the deep layer, which was unresolvable with FA images, especially since the anatomical information of the deep vasculature is lost due to retinal light scattering in FA. Therefore OCT angiography might be a better non invasive tool in detecting early FAZ changes in DR compared to FA.

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1. Introduction

Diabetic macular ischemia (DMI) is an important clinical feature of diabetic retinopathy (DR). It has been postulated that the selective loss of pericytes and thickening of the basement membrane in retinal capillaries occurs as a result of exposure to elevated blood glucose over an extended period of time **(1).**

Clinically, DMI is defined by an enlargement of the foveal avascular zone (FAZ) and paramacular areas of capillary nonperfusion **(2).**

It has been demonstrated that a large proportion (approximately 41%) of patients with DR in a tertiary hospital setting have some evidence of macular ischemia. Of note, this study demonstrated that visual

function was affected only in those with moderate to severe macular ischemia [2].

More recently, an analysis of the RIDE and RISE trials showed that patients with DMI at baseline progressed earlier to neovascular complications of DR during intravitreal ranibizumab treatment than those with normal perfusion at baseline [3].

Therefore, baseline assessment of DMI when initiating ranibizumab therapy for diabetic macular edema (DME) has clinical implications and may be of practical importance to patients and physicians when planning review schedules for reassessment of peripheral retinopathy grades for patients receiving injections.

Fluorescein angiography (FA) is widely recognized as an essential tool in the diagnosis and treatment of DR and DMI [2, 4].

Assessing the level of macular ischemia in an individual can often provide important clinical and prognostic information for the clinician in regard to disease severity and progression [3, 5].

However, despite its clinical usefulness, FA is acknowledged to have documented risks that include nausea, vomiting, itching and urticaria, and rarely, anaphylaxis [6].

In recent years, optical coherence tomography (OCT) has become widely accepted as a noninvasive means of acquiring high-resolution images of the retina that can be utilized in the treatment of retinal disease. The recent development of OCT angiography allows for the visualization of the retinal capillary layers and for the construction of microvascular flow maps [4].

This imaging of the retinal vasculature is novel, in that it is accomplished without the need for injection of fluorescein sodium dye [4, 5, 7].

Aim of the Work

In this study, we are going to evaluate the characteristics of Diabetic Macular Ischemia DMI showed on OCTA in comparison to conventional fluorescein angiography in DR patients and to highlight the utility of OCTA in detection of DMI concerning its advantages and disadvantages in comparison to fluorescein angiography.

2. Methodology

Study design: This is a prospective cross-sectional, observational study conducted in Ophthalmology Department in Al Azhar University Hospitals.

Study population: A total of 20 eyes of 12 patients, with a mean age of 57.6 years were recruited from Al Azhar University Hospitals outpatient clinic. 16 eyes belonged to 9 females, and the other 4 eyes belonged to 3 males.

A 6 eyes of a normal subject were included as a control for foveal avascular zone area measurement. 4 eyes belonged to 4 males and the other 2 eyes belonged to 2 females.

The following patients were included in our study:

Patients with a known clinical diagnosis of Diabetes Mellitus (any type), patients with Diabetic Retinopathy (in non proliferative stage).

The following patients were excluded from our study:

Patients with any systemic cardiovascular disorder such as: Hypertension - Pre-eclampsia (toxemia of pregnancy) - Emboli and thrombi - Central retinal artery occlusion - Cranial arteritis - Sickle cell disease - Carotid artery disease - Arterial spasm such as Transient Ischemic Attacks - Collagen diseases - Use of hormonal contraception, patients with significant ophthalmological comorbidities, including patients with:

Advanced macular pathologies (inherited macular dystrophy and macular degeneration or scarring of any cause), proliferative diabetic retinopathy, significant cataract (without surgical indications at the time of examination), previous retinal arterial or venous occlusion, posterior segment inflammation, patient diagnosed with glaucoma, Patients with history of previous treatment rather medical (ANTI Vascular Endothelial Growth Factor injections or Macular LASER treatment) or retinal surgical interference, patients with poor quality images, either on OCT angiography (Mainly due to eye movements) or on FA (Mainly due to media opacities) and patients who had not undergone FA due to either renal dysfunction or previous history of allergy to fluorescein dye.

Patients with DR presented to Al Azhar University Hospitals outpatient clinic, were recruited and underwent standard clinical examination and testing as appropriate for their clinical disease including:

History taking including; personal history, history of systemic diseases particularly; diabetes mellitus and hypertension, history of ocular diseases; mainly glaucoma, history of previous treatments; mainly retinal laser photocoagulation and/or intraocular injections), BCVA (using Snellen's visual acuity chart), Pupillary light reflex.

IOP measurement (using Goldmann applanation tonometer), Slit lamp examination of the anterior segment, Gonioscopy (Examination of the angle of the anterior chamber, using Goldmann three-mirror lens) for ocular hypertensive and glaucomatous eyes, Dilated fundus examination (using slit lamp biomicroscopy and indirect ophthalmoscopy).

Multimodal imaging procedures including:

Color fundus photography, Fluorescein angiography and Optical coherence tomography angiography. All were performed on the same day or during the same week.

Statistical analysis:

Data were analyzed using statistical program for social science (SPSS) version 20. Quantitative data were expressed as mean ± standard deviation (SD), median and range (minimum – maximum). Qualitative data were expressed as frequency and percentage.

3. Results

Table (1): Comparison between control group and patients group regarding demographic data

		Control group No. = 6	Patients group No. = 20	Test value	P-value	Sig.
Sex	Female Male	2 (33.3%) 4 (66.7%)	16 (80.0%) 4 (20.0%)	4.719*	0.030	S
Age	Mean ± SD Range	46.67 ± 8.14 35 – 58	57.60 ± 6.06 45 – 67	3.589•	0.001	HS
Eye	Rt Lt	4 (66.7%) 2 (33.3%)	9 (45.0%) 11 (55.0%)	0.867*	0.352	NS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; •: Independent t-test

Table (2): Comparison between control group and patients group regarding FAZ area measurements by FFA and OCTA.

		Control group No. = 6	Patients group No. = 20	Test value•	P-value	Sig.
FFA	Mean ± SD Range	0.23 ± 0.03 0.2 – 0.27	0.83 ± 0.33 0.25 – 1.6	4.400	0.000	HS
FAZ in FFA	Small (without DMI) Large (with DMI)	6 (100.0%) 0 (0.0%)	2 (10.0%) 18 (90.0%)	17.550*	0.000	HS
SCP OCTA	Mean ± SD Range	0.19 ± 0.03 0.13 – 0.23	0.45 ± 0.14 0.23 – 0.76	4.480	0.000	HS
FAZ in SCP OCTA	Small (without DMI) Large (with DMI)	6 (100.0%) 0 (0.0%)	4 (20.0%) 16 (80.0%)	12.480*	0.000	HS
Difference between FFA & SCP OCTA	Mean ± SD Range	0.04 ± 0.05 0.01 – 0.13	0.38 ± 0.29 0.01 – 1.21	2.761	0.011	S
DCP OCTA	Mean ± SD Range	0.20 ± 0.04 0.13 – 0.24	0.84 ± 0.24 0.54 – 1.46	6.627	0.000	HS
Difference between SCP and DCP OCTA	Mean ± SD Range	0.00 ± 0.00 0 – 0.01	0.39 ± 0.25 0.02 – 1	3.710	0.001	HS

*: Chi-square test; •: Independent t-test

Table (3): Comparison between control group and patients group regarding OCTA automated ETDRS – perfusion.

		Control group No. = 6	Patients group No. = 20	Test value•	P-value	Sig.
Central	Mean ± SD Range	0.10 ± 0.08 0.01 – 0.25	0.08 ± 0.02 0.07 – 0.12	1.058	0.301	NS
Inner	Mean ± SD Range	0.30 ± 0.09 0.09 – 0.42	0.24 ± 0.02 0.21 – 0.27	2.879	0.008	HS
Outer	Mean ± SD Range	0.34 ± 0.08 0.17 – 0.45	0.26 ± 0.02 0.22 – 0.29	4.231	0.000	HS
Full	Mean ± SD Range	0.33 ± 0.08 0.15 – 0.43	0.28 ± 0.03 0.24 – 0.32	2.375	0.025	S

•: Independent t-test

Table (4): Difference in FAZ area measurements by OCTA between SCP and DCP among control group and patients group.

		SCP OCTA	DCP OCTA	Difference	Test value•	P-value	Sig.
Control group	Mean ± SD Range	0.19 ± 0.03 0.13 – 0.23	0.20 ± 0.04 0.13 – 0.24	0.000	-3.450	0.018	S
Patients group	Mean ± SD Range	0.45 ± 0.14 0.23 – 0.76	0.84 ± 0.24 0.54 – 1.46	0.390	-6.949	0.000	HS

•: Paired t-test

4. Discussion

In this study, we assessed whether OCT angiography can detect changes in FAZ shape and size in comparison with FA image at the same time. Furthermore, the superficial and deep vasculature surrounding the FAZ was analyzed in DR in comparison to a healthy control group. In addition, we were interested to know if these FAZ alterations correlate with visual acuity and can be used for early screening.

SD-OCT imaging is not able to detect changes in FAZ. Currently, FA is the gold standard for the exact detection of the FAZ, without the possibility to differentiate between superficial and deep retinal vasculature [(8)].

OCT angiography is one of the first non-invasive imaging techniques capable of detecting changes in the FAZ. OCT angiography data showed that in the superficial layer of the vasculature, the mean horizontal, vertical, maximum FAZ diameter were larger in diabetic eyes than in healthy eyes. These findings correspond to our data based on funduscopy and FA.

Moreover, all of the above-mentioned findings are more obvious in the deep layer, which was unresolvable with FA images, especially since the anatomical information of the deep vasculature is lost due to retinal light scattering in FA.

Therefore OCT angiography might be a better non invasive tool in detecting early FAZ changes in DR compared to FA [(9)].

The FA-based ETDRS grading criteria capillary loss (ischemia) and leakage of fluorescein dye [(10)] are of particular relevance for clinical practice [(11)].

Focal photocoagulation, a treatment modality for diabetic macular edema (DME), targets macroaneurysms and microaneurysms with leakage in FA.

OCT angiography does not directly depict leakage, and thus does not provide information on blood–retina barrier integrity [(12)]. However, we found that the overlay of SD-OCT-derived retinal thickness mapping and OCT angiography may help to identify microaneurysms with leakage through local thickness maxima. Hence, OCT angiography might be applicable as a diagnostic tool for planning focal photocoagulation of microaneurysms with leakage [(13)]. Further research is required to support this contention.

Thus, OCT angiography of the FAZ might be beneficial for identifying early microvascular abnormalities to determine the appropriate treatment target for patients according to their risk profile. Further studies are needed to investigate the utility of OCT angiography in eyes with no or mild DR.

Although the number of eyes in the series of our study is limited, we tried to extract some **demographic information**.

A total of 20 eyes, (4 males and 16 females) included in the patient group, were identified who met the imaging criteria and 6 healthy control eyes (4 males and 2 females) were also included to be compared with the patient group. The mean age for patient group was 57.60 ± 6.06 years and for control group is 46.67 ± 8.14 years. Coloured fundus photo, FA and OCTA were done in the same day.. Maximum FAZ area size is manually measured by Image J software in FA, SCP and DCP of OCTA. Qualitative and Quantitative analysis is done to the images data.

In our study we exclude patients with any systemic vascular disease that may affect macular perfusion other than diabetes, we also exclude patients in proliferative stage of diabetic retinopathy or any previous treatment rather medical (AntiVEGF, Laser) or surgical.

We found that Statistical analysis shows that there was statistically significant difference between FAZ area size measurements by FFA and SCP in OCTA among patients group that was larger in FFA. On the other hand, no statistically significant difference was found among control group.

We also found that statistical analysis shows that there was statistically significant difference between control group and patients group regarding FAZ area size measurements in mm^2 by FFA and OCTA in (SCP & DCP) that was larger in patient group and also there was statistically significant difference between control group and patients group in differences in FAZ area measurements in mm^2 between FFA & SCP in OCTA and between SCP & DCP in OCTA in each group.

Statistical analysis shows also that there was statistically significant difference between control

group and patients group regarding inner, outer and full ETDRS perfusion map in OCTA. The vessel perfusion and density is less in patient group.

We finally found negative correlation between BCVA and FAZ area size in DCP of OCTA which was important result in our study as a prognostic sign before and after treatment.

Freiberg et al. [(14)] analyze foveal avascular zone (FAZ) dimensions and symmetry in patients with diabetic retinopathy (DR) compared to healthy controls using (OCT angiography). The FAZ is enlarged in eyes with diabetic retinopathy. Enlargement of the FAZ is correlated with reduced visual acuity. These results agree with our study results.

Garcia et al. [(15)] compared FA images with SCP of OCTA image in FAZ area size and statistical analysis also did not indicate significant difference between area measurements obtained with FA and OCTA in patients diagnosed with DMI. The same has occurred among patient without DMI regarding the measurement of normal FAZ area. This results is not agree with our study results.

Bradley et al. [(16)] compared FA image with SCP of OCTA image in FAZ area size and shape. Also FAZ area shape is graded in images of FA and OCTA by EDTRS grading protocols. Statistical analysis showed a mean of 60.4% of patients had no difference in DMI grades, 33.3% with a one-grade difference, and 2.1% with a two-grade difference between FA and OCT angiography images. A total of 4.2% of images were ungradable. These results are partially agree with our study results.

There were no relationships between the agreement in FA and OCT angiography–derived macular ischemia grades with sex, eye graded, visual acuity, DR or maculopathy grade, previous treatment with of PRP or macular laser, and anti-VEGF therapy. These results are not agree with our study results.

Hwang et al. [(17)] compared 12 individuals with normal vision serving as controls and 12 patients with various levels of DR. primary measures were parafoveal and perifoveal vessel density, total avascular area, and foveal avascular zone as detected with 6 × 6-mm OCT angiography and analyzed using an automated algorithm. Secondary measures included the agreement of the avascular area between the OCT angiogram and FA. Compared with the 12 healthy controls DR patients had reduced parafoveal and perifoveal vessel density by 12.6% and 10.4% respectively. Total avascular area and foveal avascular zone area were greater in eyes with DR by 0.82 mm and 0.16 mm^2.

Avascular area analysis with an automated algorithm using OCT angiography, although not equivalent to FA, detected DR reliably in this small pilot study. These results agree with our study results.

Conclusion

Optical coherence tomography angiography is a recently introduced imaging technology with several reports about its advantages and disadvantages.

Our study has demonstrated that OCTA may provide images with higher details regarding macular status, becoming a novel imaging technique for the diagnosis of DMI, and may become an alternative to FA for this purpose. The results also offer improved quantification of FAZ area in diabetic patients without DMI when compared to diabetic subjects with established macular ischemia.

Throughout our work, we found that optical coherence tomography angiography has mainly three advantages being noninvasive with no need for a dye, so can be done for pregnant women, patients with renal disorders and those who had previous history of adverse reactions to fluorescein dye.

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